REMARKS

Applicants would like to thank the Examiner for the interview granted the undersigned on November 12, 1996. The following discussions include arguments presented during the interview. It is also acknowledged with appreciation the withdrawal of several rejections previously of record. A sole ground for rejection remains.

Rejection of Claims 1-9, 12-22, 25-27, 29, 31 and 32 under 35 U.S.C. § 112, first paragraph

Claims 1-9, 12-22, 25-27, 29, 31 and 33 are rejected under 35 U.S.C. § 112, first paragraph because it is the Examiner's opinion that "the specification, while being enabling for a pharmaceutical composition comprising a HSV-1 or HSV-2 having a mutation in the ICP8 and ICP 28, does not reasonably provide enablement for all herpesviruses, nor any protein essential for replication, nor viruses encoding heterologous antigens" (Office Action, p. 2).

The Examiner states that the specification provides a working example of using a mutated herpes simplex and the claimed invention encompasses a multitude of herpesviruses. The Examiner in support of the rejection asserts (1) that the herpesvirus family encompasses viruses with different pathogenicity and clinical signs, (2) that the proteins required for replication have a different mode of action and structure, (3) that the specification provides a limited disclosure of those genes essential for replication, and (4) that heterologous antigens are lethal and ineffective in hosts. In view of these assertions, the Examiner concludes that one skilled in the art would be forced into undue experimentation to practice the claimed invention.

Applicants respectfully disagree. Each of these assertions will be treated under a different heading.

The specification disclosure of essential genes.

It must be kept in mind that the specification is written to the person of skill and must enable that person of skill. It preferably omits that which is well known in the art. It is with these guidelines that the PTO must analyze the disclosure of the specification.

The specification teaches, at pages 1 and 2, that the expression of genes are divided into classes (immediate early, early, late) and that several proteins are known to regulate expression of herpesvirus genes, thereby being essential for replication. At page 7, the specification teaches that the entire genomes of four herpesviruses are known (HSV-1, VZV, EBV and CMV) and that restriction maps, partial sequence and location of many genes in the remaining herpesviruses are known. It is also taught that genomic libraries are available and a large volume of plasmids are known. The specification further provides reference citations in support of these teachings.

In discussing the preferred proteins (HSV-1 ICP8 and ICP27) at page 8 of the specification, it is taught that these proteins have homologs in VZV, EBV, CMV, and/or non-human equine herpesvirus type-1.

Thus, the person of skill in the art finds significant guidance in the present specification to identify genes essential for replication in both HSV-1, HSV-2 and other herpesviruses.

As noted by Davison *et al.* as early as 1983, it was observed that the herpesviruses varicella-zoster virus (VZV) and HSV-1 possessed several conserved genes arranged colinearly in the genomes (Davison, A.J., *et al.*, *J. Gen. Virol.*, *67*:1759-1816 (1986), which is cited at page 7 of the specification and is being filed with this Response as Exhibit A). Davison *et al.* further confirmed this finding upon determination of the entire DNA sequence of VZV. As noted by Davison *et al.*:

> Comparison of the proposed arrangement of VZV genes in Fig. 2 with published HSV-1 transcript mapping data....indicates that both viruses have a similar gene layout. This view was confirmed by available HSV-1 sequence data, and allowed the functions of several VZV genes to be assigned on the basis of primary amino acid sequence homology of their products to HSV-1 proteins (Davison *et al.*, p. 1809).

In summarizing the functions and locations of 66 VZV genes, Davison *et al.* note further that:

> All but three of the functional assignments were made on the basis of HSV-1 gene location and confirmed by amino acid sequence homology with HSV-1 proteins (Davison *et al.*, p. 1809).

In addition, to the similarity found between the VZV and HS-1, Davison *et al.* also teach that:

> Approximately 30 VZV proteins are homologous to proteins predicted from the complete EBV sequence determined by Bear *et al.* (1984) (Davison *et al.*, p. 1809).

In conclusion Davison *et al.* state that:

> The way in which data from one herpesvirus may be so usefully applied to another thus encourages herpesvirologists to cultivate a more catholic approach towards the family of viruses they study (Davison *et al.*, p. 1813).

Chee, *et al.* ("Analysis of the Protein-Coding Content of the Sequence of Human Cytomegalovirus Strain AD169," *Current Topics in Microbiol. and Immunol.*, *154*:125-169, (1990), cited

at page 7 of the specification and attached hereto as Exhibit B) discusses obvious homologies between CMV and HSV-1. For example, at page 148, the article states

> A set of seven HSV-1 genes has been shown to be essential for the replication of an HSV-origin-containing plasmid. The HCMV homologs of four of these have been identified by sequence analysis. HCMV-UL54 encodes the DNA polymerase and HCMV-UL57 the major DNA-binding protein (MDBP). The latter sequence shows 72% identity over a length of 1160 aligned amino acids to the MDBP of simian CMV. HCMV-UL105 encodes a homolog to HSV-UL5, which is probably a helicase enzyme. Helicases belong to a superfamily of proteins with functions in replication and/or recombination. A nucleotide-binding site in UL105, of type GxxGxK (where x is any amino acid), is common to the other members of the superfamily..HCMLV-UL70 is the fourth HCMV gene with an obvious replication gene counterpart, in HSV-UL52... [citations omitted]

In July 1994, Baer *et al.* ("DNA Sequence and Expression of the B95-8 Epstein-Barr Virus Genome", *Nature, 310*:207-211 (1984), also cited at page 7 of the specification and attached hereto as Exhibit C) discusses the DNA sequence and expression of the B95-8 Epstein-Barr virus genome, including the early and late productive cycle genes. Baer, *et al.* identify the function of these proteins in view of the homology with known protein sequences (e.g., with HSV).

Also working with Epstein-Barr virus, Fixman, *et al.* ("trans-Acting Requirements for Replication of Epstein-Barr Virus ori-Lyt", *J. of Virology, 66*:5030-5039 (1992), Exhibit D) discusses the modes of replication of the virus during the lytic cycle and latency. The article, as do those discussed above, predicts the function of genes based upon sequence homology with HSV.

Finally, in Fields Virology, (Exhibit E), Chapter 72, reviews the replication of the herpes simplex virus which includes HSV gene expression, function and organization. In

Table 1 of the chapter, 36 HSV genes and gene products essential for replication are described and identified. The Examiner acknowledged in the interview that the rejection, to the extent that it is based upon the breadth of the replication essential proteins and genes, will be withdrawn in light of the teachings of this reference.

Each of these references, as well as others cited in the specification, establish a fraction of the background knowledge available to the person of skill in the art. The specification, which cannot be considered in a vacuum but in light of that which is known in the art, provides significant disclosure and guidance as to those genes which can be mutated to render members of the herpesvirus, including viruses other than HSV-1 and HSV-2, replication defective. The references establish that many genes and gene products of the members of the herpesvirus families are homologous, that the person of skill in the art accepts this homology as being an indication of similarity in function, and that many genes and gene products are essential for replication.

Proteins having a different mode of action and structure.

It is agreed that, in general, different proteins have different functions. However, the particular function of the protein selected for mutation in the claimed invention is irrelevant. The critical factor is whether the protein is essential for replication. If it is, then, by definition, its inactivation (either by mutation or deletion) will render the mutant replication-defective. The critical property in this context is whether the mutated virus will replicate while still expressing sufficient antigens to induce an immune response, not whether, for example, a specific helicase activity is still present.

The specification verifies this assertion in that the inactivation of three out of three essential genes resulted in a functional mutant (ICP4, ICP8 and ICP27). Having the ICP4,

ICP8 and ICP27 data available to them, one of skill in the art would expect that the inactivation of other essential proteins would produce similar results. Please note that immunity to the herpesvirus is induced by proteins which are expressed, not the protein(s) which is/are not expressed. The Examiner has presented no teaching or scientific reasoning to suggest that other mutants would not function similarly.

Herpesviruses possess differences in pathogenicity and etiology.

It is true that not all members of the family of herpesviruses are identical and they can differ in pathogenicity and clinical signs. Of course, members of a family always differ in some manner. However, it is not clear precisely why this observation supports a rejection. Note that the members of the family have significant similarities, as evidenced by the fact that they have been classified together, possess similar genomes and similarities in pathogenicity and etiology. Applicants have established with working examples that two members of the family (HSV-1 and HSV-2) were successfully mutated and induced a protective response. Applicants have provided sufficient teachings to the person of skill in the art how to make others and the person of skill in the art would reasonably expect these mutants to also induce a protective immune response. Each mutated herpesvirus employed in the present invention will have basic common properties, they will be replication-defective and will express other viral proteins which will induce an immune response. The actual function of those expressed viral proteins which will define the pathogenicity and etiology of the virus (or the non-mutated virus) are generally of little concern to the success of the invention. The Examiner has failed to provide any technical basis for supporting a contrary conclusion.

Heterologous antigens are lethal to and ineffective in hosts.

The Examiner concludes the rejection with an assertion that since heterologous antigens are lethal to hosts and foreign antigens are known not to be expressed in a sufficient level or proper formation to be protective in a vaccine. This rejection appears to be applicable against Claims 31 and 36, only.

Expression of foreign genes in vaccines are routine, as set forth in Fields Virology (Exhibit F). See, for example, Chapter 16, p. 489 "Recombinant vaccinia viruses expressing the protective antigen (or antigens) of a large number of viruses have been constructed and shown to be protective in experimental animals." In this case, the present mutated herpesviruses will induce an immune response against the herpesvirus as well as an immune response against the heterologous antigen. The manufacture of such a mutant is enabled and can be made, for example, employing the technique described in the working example described at pages 55-58 of the specification where a foreign gene was expressed in a replication-defective HSV-2. As such, the Examiner's assertion is unfounded and technically incorrect.

Dependent Claims do not stand or fall with the Independent Claims

The Examiner has rejected all of the claims together. It is noted that the Examiner does not discuss Claims 33-36. Applicants disagree that the dependent claims should be considered to stand or fall with the independent claims as they differ significantly in scope.

Claims 4, 8, 15, 21, 27, 29, and 35 are of the scope the Examiner has identified in the rejection as being enabled (i.e., mutations in the ICP8 and ICP27 genes of the herpes simplex viruses). Thus, the rejection of these claims should be withdrawn.

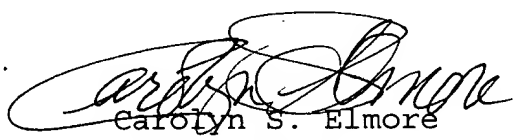
Claims 3, 7, 14, 20 and 34 define the herpesvirus to be HSV-1 or HSV-2. As Applicants have established that the person of skill in the art is aware of 36 HSV-1 genes or proteins essential for replication, and that HSV-2 is closely related to HSV-1, the specification is enabling for the manufacture and use of mutants which inactivate other essential genes. The examiner appeared to be in agreement with this conclusion in the interview.

Claims 1, 2, 5, 6, 9, 12, 13, 16, 17, 18, 19, 25, 26, 31, 32, 33 and 36 expand the scope of the herpesvirus. As established by the articles enclosed in Exhibits A-F, each of these family members are closely related and possess many homologous genes. The genomes of several family members have been fully or partially sequenced and characterized. The teachings of the present specification can be readily applied to other members of the family without undue experimentation and with a reasonable expectation of success. As such, the specification enables the full scope of the claims.

Summary

It is respectfully submitted that the claims are now in condition for allowance. If the Examiner feels that a telephone conference would be helpful in expediting the prosecution of the application, the Examiner is encouraged to telephone the undersigned at (617)861-6240.

Respectfully submitted



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